# Levalbuterol Versus Albuterol

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Albuterol has been used for more than 40 years to treat acute asthma exacerbations as a racemic mixture of isomers: the active form, (R)-albuterol, or levalbuterol, and (S)-albuterol, classically considered inert. The single-isomer formulation, levalbuterol, has been synthesized recently and used therapeutically when the racemate is deemed less desirable. Basic investigations indicate that racemic albuterol and levalbuterol can produce effects that favor asthma remediation, including corticosteroid amplification and reduction of inflammatory mediators; in contrast, (S)-albuterol produces opposite effects. With inhalation of racemic albuterol, circulating (S)-albuterol persists 12 times longer than levalbuterol, suggesting potential for paradoxical effects observed clinically. Although mainly consistent with basic findings, clinical studies suggest no overwhelming superiority of levalbuterol over racemic albuterol; however, levalbuterol's effects may be greatest in moderate to severe asthma patients, especially with racemic albuterol overuse. Recent adoption of the hydrofluoroalkane formulation has narrowed the cost gap between levalbuterol and racemic albuterol metered-dose inhalers, but it remains for the nebulized formulations. Thus, physician selection of these drugs has remained dependent on experience, pharmaceutical knowledge, and established prescribing habits combined with cost factors, formulary structures, and availability, such that racemic albuterol is still used significantly compared with levalbuterol to treat acute asthma exacerbations.

## Introduction

Asthma is a pulmonary disease characterized by reversible airway obstruction and inflammation that occurs in 8% to 10% of the population worldwide [1]. As currently characterized, asthma severity is associated with frequency of exacerbations and disruption of quality of life [2]. Mainstay therapy for asthma includes the use of $\beta_2$-receptor agonists for reversal of acute airway obstruction and asthma exacerbations such as cough. Thus, up to two thirds of asthma patients in the United States and United Kingdom have received $\beta_2$-receptor agonist therapy during the past 20 years [3,4].

Albuterol (or salbutamol, as it is known outside the United States), the most widely used $\beta_2$-agonist for asthma, has an efficacy, safety, and selectivity profile that makes it the drug of choice as rescue therapy for acute asthma exacerbations and symptoms. Racemic albuterol (historically and currently marketed simply as albuterol, or salbutamol) is a 50:50 racemic mixture of the active isoform, or eutomer, (R)-albuterol, or levalbuterol, and the stereochemically opposite distomer, (S)-albuterol. Because $\beta_2$-adrenoreceptors in the body are also stereospecific for ligand binding, levalbuterol binds with 100 times greater affinity than (S)-albuterol, promoting effects associated with $\beta_2$-adrenoreceptor ligation more profoundly [5]. Because of this phenomenon, (S)-albuterol is classically inert as compared with levalbuterol. Thus, it is well accepted that the desirable effects of racemic albuterol in the treatment of asthma all originate from levalbuterol within the racemate.

However, some asthma patients experience "paradoxical worsening" of asthma symptoms with continued use or overuse of racemic albuterol and other $\beta_2$-agonists, with death occurring in some instances [6–8]. The causes of these paradoxical phenomena remain unclear; however, evidence from basic preclinical studies [9] and some relevant clinical studies suggests that racemic mixtures of albuterol isomers may contribute to these phenomena, which may originate from (S)-albuterol. In this regard, one important characteristic of (S)-albuterol is its slower pharmacokinetic profile (it is metabolized as much as 12 times slower than levalbuterol) [10,11]. This occurs in part because of its delayed sulfation and elimination by enzymes preferentially specific for levalbuterol [12–15], which results in differences in circulating levels of each isomer after administration of racemic albuterol [16]. It has been shown that circulating levalbuterol is undetectable within 2 to 3 hours after a single dose of inhaled racemic albuterol, whereas (S)-albuterol levels persist for as long as 12 hours and may be preferentially retained in the lungs [17,18]. Thus, there are good reasons to consider the separate physiologic and pharmacologic effects of each isomer within the racemate, as well as levalbuterol

alone, when mechanisms and therapy for asthma using short-acting $\beta_2$-receptor agonists are considered.

## Stereochemistry of Albuterol

As mentioned previously, the active isoform of albuterol is (R)-albuterol (R stands for rectus), which defines it as having its constituents bound to a chiral carbon arranged in a clockwise, or "right-hand-turning," order of mass number priority in the order of the following: 1) the catechol ring, 2) the amino-containing aliphatic chain, and 3) the hydroxyl group. On the other hand, the "inactive" distomer, (S)-albuterol (S stands for sinister and is the nonsuperimposable mirror image), has these same molecular constituents bound to the chiral carbon in the reverse, counterclockwise, or "left-hand-turning," order [19,20]. All chiral carbon–containing molecules such as these are also typically distinguished by the D- and L- designations, which indicate the ability of their solutions to rotate polarized light in one direction or the other. Thus, the D- designation indicates a dextrorotatory, or right-handed optical rotation, of polarized light, whereas the L- designation indicates a levorotatory, or left-handed rotation, of polarized light. These mass order–based ([R]-/[S]-) and light rotation–based ([D]-/[L]-) nomenclatures are distinct and not always consistent with each other for all chiral carbon–containing molecules. For example, for β-agonists, the mass order–based (R)- designation applies to compounds having solutions that rotate polarized light to the left and therefore have a light rotation–based (L)- designation. The opposite is true for their distomers, having the (S)- mass order–based designation while rotating polarized light to the right and having a (D)- light rotation–based designation. For this reason, (R)-albuterol is also known as levalbuterol by common convention, while (S)-albuterol would be known as dexalbuterol, a term that is seldom used.

The effectiveness of the eutomer, levalbuterol, within the racemate is dependent on its similarity of molecular structure to (-)epinephrine, a β-adrenoreceptor ligand synthesized naturally by the adrenal medulla and having a (-) isoform designation in the older nomenclature. In this case, the older nomenclature assigned (+) for solutions of compounds that rotated polarized light to the right and were dextrorotatory and (-) for solutions of compounds that rotated polarized light to the left and were levorotatory. Thus, as mentioned previously, the primary therapeutic effect of racemic albuterol is caused by the levalbuterol within the drug mixture, which is mediated through stereoselective binding to the $\beta_2$-adrenoreceptors on airway smooth muscle (ASM) cells [20,21], promoting relaxation, airway dilation, and a decrease in resistance to airflow into the lungs.

## Preclinical Studies of Levalbuterol: Airway Contractility

### Overview

Many studies have pointed out the well-established effects of racemic albuterol in promoting airway relaxation, which are caused by levalbuterol within the racemate. Because the availability of albuterol isomers is relatively recent, fewer studies have been conducted on single-albuterol isomers. However, as mentioned previously, the production of single isomers in sufficient quantities and purities for experimentation led to recent (since 1996) studies of single isomers. Overall, single-isomer and racemate comparison studies indicated the following: 1) levalbuterol effects occur because of $\beta_2$-adrenoreceptor ligation-dependent mechanisms, as expected; 2) there is sufficient levalbuterol in racemic albuterol to produce effects through the same mechanism, as expected; 3) the effects of (S)-albuterol are frequently the opposite of those of levalbuterol; 4) the effects of levalbuterol are often blunted in the presence of (S)-albuterol; and 5) (S)-albuterol can inhibit the anti-inflammatory effects of corticosteroids.

### Airway contractility in animal tissue/cellular models

Several important studies have been carried out in tissues and cells from animals to collect data on potential mechanisms that are not typically obtainable in human tissue. Collectively, across in vitro models of ASM from several species investigated (eg, horse, cow, guinea pig, and mouse), administration of levalbuterol alone was found to relax ASM; decrease ASM intracellular calcium levels; decrease the frequency of ASM intracellular calcium oscillations and calcium sensitivity; and suppress ASM contractions produced by carbachol, histamine, and allergen (ovalbumin) [22–25]. In contrast, several of those studies also showed that (S)-albuterol increased intracellular calcium levels; significantly increased the contractile response elicited by carbachol; and increased intracellular levels of inositol-1,4,5-triphosphate, a key intermediate in the muscarinic $M_3$ receptor signaling pathway that produces ASM contraction. Furthermore, the (S)-albuterol–associated increases in intracellular calcium were inhibited by atropine and were insensitive to the $\beta_2$-adrenoreceptor inverse agonist ICI–118,551. Thus, findings from several studies suggested that some (S)-albuterol effects may be independent of ligation of the $\beta_2$-adrenoreceptor, possibly acting through the muscarinic $M_3$ receptor. Furthermore, in equine tracheal tissue strips, (S)-albuterol had prejunctional effects that promoted acetylcholine release from parasympathetic neurons, representing an additional potential cholinergic mechanism through which (S)-albuterol may counteract the $\beta_2$-adrenoreceptor–mediated effects of levalbuterol [23]. Given that one study demonstrated that both (S)-albuterol and racemic albuterol increased intracellular calcium levels [26], the concept that (S)-albuterol within the racemate can contribute to paradoxical effects of racemic albuterol was supported.

### Airway contractility in whole animal models

While the tissue/cellular studies have been informative regarding potential mechanisms of isomers and racemates of albuterol, whole animal studies have provided insights into integrated functional ramifications of mechanisms,

and data consistent with the in vitro results. In guinea pigs—an important animal model because of the species' histamine-based allergic responses that are similar to those of humans—administration of racemic albuterol and (S)-albuterol increased bronchial hyperresponsiveness to histamine and other spasmogens [27,28]. For example, acute subcutaneous injection of racemic albuterol for 1 hour mitigated allergic bronchospasm promoted by ovalbumin [27]. However, longer infusions of racemic albuterol led to increasing responsiveness to spasmogens that culminated in death within 48 hours of infusion in most animals.

Interestingly, the loss of bronchoprotection with racemic albuterol may have been associated with (S)-albuterol within the mixture because a 1-hour infusion of (S)-albuterol alone promoted a significant increase in airway resistance. These data are supportive of the idea suggested previously that adverse effects of (S)-albuterol can predominate with continued administration of racemic albuterol over time [27]. It is of further interest that in considering the tissue/cellular studies cited above, the adverse effects of (S)-albuterol could be prohibited by sectioning of the vagus nerve, further suggesting possible involvement of muscarinic pathways associated with (S)-albuterol effects.

Although mouse allergic responses are based more within serotonergic pathways, as opposed to histaminic pathways in guinea pigs [29], it is interesting that findings in a murine model of asthma were consistent with those reported in guinea pigs in that again, (S)-albuterol increased airway hyperresponsiveness to methacholine in mice with allergic airway inflammation induced by ovalbumin [30]. However, while murine models are popular for the study of allergic airway inflammation and hyperresponsiveness, it is worth noting that there are no published studies of the effects of inhaled albuterol isomers on airway contractility in mice, which should be undertaken to better understand the functional mechanisms of action of racemic and (S)-albuterol.

### Airway contractility in human tissue/cells

To date, there are only a few published studies of contractility influences of albuterol isomers in human airway tissue and cells; however, the results are consistent with the findings in animal tissues and cells cited above. For example, a study in human ASM cells in culture indicated that levalbuterol can decrease intracellular calcium, whereas (S)-albuterol increased intracellular calcium levels in a concentration-dependent manner [31]. Presumably, these effects are associated with ASM relaxation and contraction, respectively. In fact, in one comprehensive study of human airway tissue, levalbuterol reduced the sensitivity and response amplitude to the spasmogens methacholine and histamine, whereas (S)-albuterol enhanced contractility in response to histamine, leukotriene $C_4$, and IgE [32]. Importantly, these data are consistent with those obtained in animal tissue/cells [22,24,26] and support the idea that (S)-albuterol may exacerbate ASM contraction in the presence of spasmogens and/or when levalbuterol from administration of a racemic mixture is metabolized and no longer present, as mentioned above.

## Preclinical Studies of Levalbuterol: Airway Inflammation

### Overview

Aside from the well-known effects of albuterol on ASM relaxation outlined above, albuterol has been shown to decrease proinflammatory cytokine release, possibly through cyclic adenosine monophosphate (cAMP)-associated modulation of nuclear transcription factors IκB and nuclear factor-κB (NF-κB). These are known to play a critical role in regulating proinflammatory chemokine and cytokine message transcription and the eventual production of their proteins [33,34]. Furthermore, intracellular events consequent to $\beta_2$-adrenoreceptor ligation can influence glucocorticoid receptor complex formation and upregulation of the cell-cycle inhibitor protein $p21^{(Waf1/Cip1)}$, which in turn can diminish cell proliferation [35]. Such effects likely are responsible for the apparent anti-inflammatory synergy between $\beta_2$-adrenoreceptor agonists and corticosteroids [36] and may be among the mechanisms behind the success of current $\beta_2$-adrenoreceptor agonist and steroid combination therapies in asthma [36,37].

### Anti-inflammatory effects in immune cells

The effects of albuterol isomers have been studied in immune cells expressing $\beta_2$-adrenoreceptors, such as T lymphocytes, eosinophils, and mast cells, from human and animal sources. (S)-albuterol increased histamine release and interleukin (IL)-4 mRNA and protein in murine mast cells [38] but had no effect on eosinophil peroxidase release from eosinophils from allergic and nonallergic patients, even though levalbuterol and racemic albuterol inhibited peroxidase release [39]. However, another study suggested that levalbuterol and racemic albuterol inhibited superoxide production of IL-5–activated human eosinophils, whereas (S)-albuterol increased superoxide production [40].

A study of human T cells showed an important property of albuterol isomer interaction in that addition of (S)-albuterol progressively diminished the suppressive effects of (R)-albuterol on T-cell proliferation, and these effects were inhibited by propranolol, suggesting that they occurred through ligation of the $\beta_2$-adrenoreceptor [41]. Furthermore, levalbuterol also decreased T-cell release of proinflammatory cytokines IL-2, interferon-γ, and IL-13, whereas (S)-albuterol significantly increased release of IL-2 and IL-13 [41]. Thus, although there appears to be some heterogeneity of findings within human eosinophils, the effects of levalbuterol seem mainly anti-inflammatory, whereas (S)-albuterol can be considered mainly as promoting inflammation alternatively on its own or in opposition to levalbuterol in immune cells. In fact, these studies and others led to the idea that (S)-albuterol

could be functioning as an "inverse agonist," opposing the $\beta_2$-adrenoreceptor agonist properties of levalbuterol [41–43].

### Anti-inflammatory effects in ASM cells

It has become apparent in recent years that ASM cells have signal-secreting ability in addition to their contractile function, because they release important cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, and IL-11 [44,45] and therefore may be important modulators of airway inflammation [46]. In the case of GM-CSF, ASM can be stimulated to secrete significant amounts of this cytokine, which is known for its ability to promote eosinophil activation and survival [47,48]. One important study in human ASM cells demonstrated the following attributes of albuterol isomers: 1) levalbuterol reduced GM-CSF release and amplified the effect in combination with dexamethasone; 2) (S)-albuterol, similar to propranolol and ICI–118,551, increased GM-CSF release and nullified the effect of dexamethasone; 3) incremental addition of (S)-albuterol to levalbuterol diminished levalbuterol-associated GM-CSF effects; and 4) effects of levalbuterol were inhibited with addition of propranolol, suggesting the reversal of levalbuterol effects through the $\beta_2$-adrenoreceptor [49]. These results are similar to those cited above in T cells [41], giving credence to the idea that ASM may serve an immunomodulatory role that is influenced by ligation of the $\beta_2$-adrenoreceptor. The similarity of ASM results obtained with (S)-albuterol in comparison with propranolol, and especially with ICI–118,551, further supports the idea that (S)-albuterol may be acting as an inverse agonist. In addition, the negative influence of (S)-albuterol on the ability of a corticosteroid to suppress proinflammatory cytokine release is of some concern and may have translational relevance in consideration of the β-agonist paradox and formulations of steroids with racemic $\beta_2$-adrenoreceptor agonists.

Prior studies showed that racemic β-agonists induce elevations in cAMP, resulting in reduced GM-CSF release by human ASM cells [50,51], presumably caused by levalbuterol within the racemate binding to the $\beta_2$-adrenoreceptor. Consistent with that notion, administration of levalbuterol increased intracellular cAMP levels, likely driven by observed increases in stimulatory G-protein expression [31]. Conversely, (S)-albuterol has been shown to increase inhibitory G-protein expression and reduce intracellular cAMP levels, as well as to increase both phosphatidylinositol-3-kinase and NF-κB activation [31], which would support synthesis and release of proinflammatory cytokines. Subsequent study in human ASM cells indicated that the cytokine suppressive effects of levalbuterol may occur as a result of the influence of phosphatidylinositol-3-kinase in decreasing the phosphorylation of IκBα, and in turn, decreasing the release of NF-κB from the IκB/NF-κB complex [52•]. Thus, there appear to be plausible intracellular mechanisms through which the opposing effects of albuterol isomers on cytokine release can be explained.

### Anti-inflammatory effects in whole animal models

Only a few studies have been published on use of levalbuterol in the treatment of airway inflammation in whole animals. One study of albuterol isomers administered from surgically implanted miniosmotic pumps in mice with allergic airway inflammation showed that levalbuterol decreased airway and parenchymal eosinophilia, goblet cell hyperplasia, bronchoalveolar lavage IL-4 levels, and plasma IgE [30]. (S)-albuterol administration in that same study increased lung tissue edema and airway hyperresponsiveness; however, it also had similar effects as levalbuterol on the variables mentioned above [30]. A subsequent study conducted in a similar fashion suggested that levalbuterol reduced histologic evidence of airway inflammation; however, decreases in bronchoalveolar lavage eosinophils and serum IgE were not statistically significant [53].

Some of the unexpected similarity of effects of levalbuterol and (S)-albuterol in whole animal models may be caused by the method of peripheral administration of the isomers, suggesting the necessity of investigations with direct aerosolized administration of inhaled isomers. The only published study of the effects of inhaled aerosolized racemic and isomeric albuterol on airway inflammation was carried out in rats with respiratory syncytial virus–associated airway inflammation in which levalbuterol administered at clinically relevant doses (0.31–1.25 mg) decreased and ultimately abolished neurogenic extravasation [54]. Conversely, (S)-albuterol had no significant inhibitory effect up to 1.25 mg, and racemic albuterol demonstrated a blunted inhibitory effect compared with levalbuterol alone, presumably because of the effects of (S)-albuterol within the racemate [54]. Thus, these data from a whole animal study of inhaled albuterol isomers are consistent with the divergence of effects observed in the more reduced studies of levalbuterol and (S)-albuterol cited above. However, the relative paucity of data in whole animal models of airway inflammation suggests that further study of inhaled albuterol isomers is needed to further our understanding of how these drugs work in the context of allergic airway inflammation.

## Human and Clinical Studies of Levalbuterol

### Basic human studies

Several small ($n < 33$) basic human studies have been conducted with albuterol isomers since they became available in 1996; however, results have been somewhat heterogeneous. For example, in one initial study, levalbuterol suppressed methacholine-induced bronchospasm more effectively than racemic albuterol and (S)-albuterol [55], which is expected based on the results from animal and human tissue and cell models cited above. Subsequent studies reported equivalencies of levalbuterol to racemic albuterol, with some indicating that the bronchodilatory effect of levalbuterol, 1.25 mg, was equivalent to that of racemic albuterol, 2.5 mg, with (S)-albuterol having little measurable effect [56–58]. In one unique study of isocap-

nic bronchoprovocation with cold air, levalbuterol had no favorable effects over racemic albuterol [59], further suggesting equivalence of effect of the levalbuterol single isomer and levalbuterol within the racemate.

However, a common theme of the above basic studies in humans was the short-term nature of the experiments (< 3 hours over 1–7 days), typically obtained after a single administration of each respective albuterol formulation. Because of the effects of levalbuterol within the racemate, such a short-term approach would be expected to show equivalently strong effects of levalbuterol and racemic albuterol and possibly no discernable effect of (S)-albuterol, especially because of the known 100-fold difference in $\beta_2$-adrenoreceptor affinity between levalbuterol and (S)-albuterol [5]. Although those studies demonstrated the expected effects of levalbuterol and racemic albuterol, their approach does not provide an assessment of differences between racemic albuterol and albuterol isomers with chronic use. Such an assessment requires additional administrations and longer intervals of exposure because of the known differences in metabolism of levalbuterol and (S)-albuterol within the body [17]. Thus, performance of longer trials is desirable to better discern the effects of (S)-albuterol under chronic conditions because it has been shown that severe asthma patients (who are more likely to use their racemic albuterol inhaler frequently) can have two to five times higher levels of (S)-albuterol in their plasma [60]. Also, steroid-naïve asthma patients have high serum levels of (S)-albuterol compared with steroid-treated asthma patients and healthy volunteers [14,16], again perhaps because of issues related to control of asthma symptoms.

### Human clinical trials in controlled asthma

One of the landmark clinical trials comparing levalbuterol and racemic albuterol was that of Nelson et al. [61], in which more than 350 adolescent and adult patients were randomly assigned to levalbuterol, 0.63 or 1.25 mg, or racemic albuterol, 1.25 or 2.5 mg. The design of this trial provided two equivalent mass levels of levalbuterol, with and without (S)-albuterol present. The results indicated significantly greater improvements in forced expiratory volume in 1 second ($FEV_1$) in the levalbuterol groups compared with the dose-equivalent racemic groups at first dosing, which diminished after 4 weeks of three administrations per day. Interestingly, the dose that provided numerically equivalent bronchodilation as that seen with 2.5 mg of racemic albuterol was 0.63 mg of levalbuterol, not 1.25 mg of levalbuterol (the mass equivalent dose), as would be expected if only levalbuterol were active within the racemate. Thus, the data of the Nelson et al. [61] study have been interpreted as showing a detrimental effect of (S)-albuterol; however, some have challenged those interpretations [62]. Unfortunately, some clinicians have interpreted the results as indicating that one simply needs to use twice as much racemate to get the same effect as the single isomer. However, this would compound the potential for a detrimental (S)-albuterol–associated effect, particularly based on the negative effects of (S)-albuterol observed in the preclinical investigations and the longer pharmacokinetic profile of (S)-albuterol cited above. Furthermore, a subsequent post hoc analysis of data from the Nelson et al. [61] study supported the idea that levalbuterol actually provided greater bronchodilation compared with the same mass quantity of (R)-albuterol within racemate [63]. Even so, the design of the Nelson et al. [61] trial, which was not powered to demonstrate superiority of levalbuterol, and the post hoc, rather than targeted primary end point analysis, have yielded only a suggestive interpretation that (S)-albuterol within the racemate may diminish the effects of levalbuterol in some asthma patients.

In a double-blind, crossover comparison study of relative efficacy using a design developed to assess the therapeutic ratio of racemic albuterol and levalbuterol, levalbuterol was, as expected, twice as effective as racemic albuterol for efficacy measures that included $FEV_1$ improvement, as well as safety measures such as change in heart rate and serum potassium concentration [64]. Although this would be the expected difference based on the mass of levalbuterol in each case, it bears consideration that the results of the study indicated that (S)-albuterol and placebo were equivalent and that levalbuterol and racemic albuterol were considered equivalent. Thus, from that study, it was concluded that levalbuterol afforded no increase in therapeutic index over racemic albuterol. Again, however, the study was designed only to demonstrate safety and efficacy from an equivalency perspective, as opposed to testing for superiority of levalbuterol versus racemic albuterol. Several clinical studies of levalbuterol have been conducted in pediatric asthma patients.

One study comparing levalbuterol to racemic albuterol in a randomized, placebo-controlled comparator trial reported no significant differences between the drugs with respect to $FEV_1$ [65]. However, it is important to note that this study was powered for efficacy versus placebo and not to discriminate among the treatment groups [65]. In another study of 338 pediatric patients, investigators focused on the primary end point of lung function as $FEV_1$ in a double-blind, placebo-controlled, randomized trial of levalbuterol, 0.31 and 0.63 mg, versus racemic albuterol, 1.25 and 2.5 mg, each administered three times per day. They found no difference in bronchodilation in any arm of the study and could demonstrate no dose–response relationship in children with mild to moderate asthma [66]. In contrast, their comparison of safety indices suggested that only levalbuterol, 0.31 mg, was similar to placebo; therefore, the authors concluded that there was a safety advantage of using levalbuterol, 0.31 mg, as a starter dose for treatment in children. Interestingly, a dose–response relationship was observed for levalbuterol only in children with more severe asthma, suggesting that with more severe disease, increased dosing of levalbuterol may be useful in treatment. However, it bears consideration

that the primary limitation of that study was that a dose dependency for the primary outcome variable (change in $FEV_1$) was not demonstrable in the entire population of children studied.

### Human clinical trials in acute/emergent asthma

Patients suffering from acute asthma attacks and/or significant exacerbations frequently present to the emergency department (ED) for treatment. To deal with this, many hospital EDs use a stepped albuterol therapeutic approach to break the cycle of breathlessness and/or coughing and begin the institution of some mode of controller therapy, such as corticosteroids. Thus, it is reasonable that studies of levalbuterol versus racemic albuterol would be undertaken in this setting.

In one study of 547 patients presenting to the ED with asthma, investigators compared levalbuterol with racemic albuterol in a randomized, double-blind, age-stratified trial design (either < 6 years old or 6–18 years old) [67]. In this study, patients were managed using a standardized asthma care albuterol treatment algorithm of 1.25 mg levalbuterol versus 2.5 mg racemic albuterol (ie, 1.25 mg levalbuterol + 1.25 mg [S]-albuterol) administered every 20 minutes for up to 2 hours, with the primary outcome being hospital admission rate [67]. Although there were no significant differences in demographic or clinical characteristics of the cohort studied (ie, race, gender, and use of controller medications, although significantly more patients randomly assigned to levalbuterol were on cromolyn [68% vs 42%]), patients administered levalbuterol had significantly fewer hospitalizations compared with those treated with racemic albuterol (35% vs 45%). Furthermore, in patients receiving more than three albuterol aerosol treatments plus oral corticosteroids, the relative risk of hospital admission was reported as 1.34 in patients treated with racemic albuterol compared with levalbuterol, which suggests that patients presenting to the ED with more severe asthma may benefit from levalbuterol compared with racemic albuterol therapy for their acute asthma exacerbations.

Some subsequent studies of asthma treatment in the ED have supported the idea that levalbuterol could be preferable to racemic albuterol in the emergent treatment of acute asthma [9,68••]. Importantly, those studies also reported assessments of plasma (S)-albuterol levels, which were inversely correlated with both $FEV_1$ on admission to the ED and the response to subsequent bronchodilator administration in the ED. Other aspects of those studies suggest that patients with high (S)-albuterol plasma levels have slower improvement in $FEV_1$ and a greater likelihood of hospital admission, whereas patients given levalbuterol have a more rapid improvement in $FEV_1$ compared with those given racemic albuterol [68••].

However, several smaller ($n$ = 70–140) pediatric asthma ED clinical studies reported no difference between racemic albuterol and levalbuterol for primary outcome measures, which included $FEV_1$, oxygen saturations, respiratory rates, peak flow rates, and length of ED stay in some studies, or secondary outcomes, which included number of treatments, length of ED stay, and hospital admission rates in others [69–71]. Some of the acknowledged study limitations included study size [69] and the inability of some children to perform reliable pulmonary function tests [71], whereas other limitations included confounding variables such as additional administration of steroids and ipratropium during albuterol treatment [69,71], administration of racemic albuterol at four times the dose of levalbuterol (5 mg racemic albuterol vs 1.25 mg levalbuterol) [70], administration of ipratropium only to the racemic albuterol group [70], and exclusion of study participants who had taken levalbuterol but not racemic albuterol [71]. These confounds make it difficult to evaluate the meaning of the results of those studies; however, most agree that further research is necessary.

## Future Therapeutic, Patient, and Cost Considerations

Consistent with the preclinical and clinical characteristics reported for levalbuterol, its use for treatment of acute asthma attacks and/or exacerbations in the ED has been associated with decreased hospitalization and, subsequently, reduced costs of follow-up medical care [72]. However, the purchase cost differential between racemic albuterol and the more expensive levalbuterol has remained a problem for widespread acceptance and use of levalbuterol in place of the racemate in all asthma treatment situations that call for albuterol. In the future, especially in well-developed countries such as the United States and the United Kingdom, it is likely that cost relevance that includes all cost factors, in addition to purchase price, will become most important, particularly in managed care hospital settings. For example, it has been reported that significant in-house hospital cost savings related to reductions in length of stay, breakthrough nebulizer treatments, and routine albuterol nebulizer administrations are achievable using levalbuterol instead of racemic albuterol [73–75]. Thus, it will be the demonstration of either cost savings, as above, or cost equivalence, as demonstrated in a subsequent study [76], that will help to determine how and how rapidly levalbuterol will replace racemic albuterol for the treatment of asthma and chronic obstructive pulmonary disease in the years ahead.

Another important factor in the selection of levalbuterol versus racemic albuterol may relate to patient satisfaction with treatment. For example, by way of survey, parents of children with asthma preferred levalbuterol in 27 of 28 important treatment evaluation categories as compared with racemic albuterol, despite the price difference [77]. Although it is important to consider that the study focused on parental motives and expenditures that are possibly indicative of treatment approaches and approval, with lesser considerations of costs not easily comparable with routine in-house treatment or emergent, indigent, or low-income cases, these data remain intriguing.

There are also important cost-related and patient perception aspects to the considerable indirect societal and personal/familial costs (eg, time lost from work, premature death, and the stigma of breathing problems with a serious disease) that are associated with asthma and its potential undertreatment [78,79]. These personal and socioeconomic factors may also require consideration in the physician's choice of levalbuterol over racemic albuterol in specific therapeutic situations.

Finally, one unexpected development relating to the cost differential between levalbuterol and racemic albuterol has grown out of the mandate of the recent Montreal Protocol Agreement for removal of chlorofluorocarbon-based albuterol metered-dose inhalers from the market to protect the environment [80]. This mandate resulted in implementation of hydrofluoroalkane (HFA)-based metered-dose inhalers, which are up to four times more expensive than the chlorofluorocarbon-based formulations. Because the levalbuterol metered-dose inhaler has only been marketed in an HFA formulation, its cost remains as before. However, with these mandated HFA formulations, the price gap between racemic albuterol and levalbuterol has narrowed, such that the purchase cost differences are likely to become less of a consideration in their selection for therapeutic use in the future. Thus, the interrelationship of all the factors outlined above, in conjunction with continued investigation of basic and clinical effectiveness, will likely influence the preferred selection of levalbuterol versus racemic albuterol for the treatment of asthma and chronic obstructive pulmonary disease in the future.

## Conclusions

Data from a substantive number of preclinical studies indicate the following: 1) levalbuterol is responsible for all the desired pulmonary β-agonist activity within racemic albuterol, which includes bronchodilation and anti-inflammatory activity; 2) metabolism of (S)-albuterol is much slower than that of levalbuterol, which can result in accumulation of (S)-albuterol with repeated use of racemic albuterol; 3) (S)-albuterol administered alone is not inert, in fact can promote bronchoconstriction, and has proinflammatory properties; 4) (S)-albuterol in the presence of levalbuterol can negate the bronchodilatory and anti-inflammatory properties of levalbuterol; and 5) (S)-albuterol can negate the anti-inflammatory effects of corticosteroids but may also require higher doses of corticosteroids to counter its negative effects.

Results from some basic human studies and clinical trials of levalbuterol versus racemic albuterol are consistent with preclinical findings and expectations based on (S)-albuterol characteristics; however, others are not, in part because of confounding variables and study design shortcomings. It is important to consider that most of the clinical trials conducted on levalbuterol versus racemic albuterol were underpowered and could not demonstrate statistically significant differences between the treatments. A consistent theme from the preclinical and clinical investigations appears to be that more severe asthma may be better treated with levalbuterol rather than racemic albuterol. This may be particularly true if chronic racemic albuterol use and/or lack of appropriate asthma controller therapy are known problems in their presentation.

Furthermore, several of the clinical studies cited above also reported that levalbuterol did not produce cardioacceleration in comparison with racemic albuterol and may be preferable for asthma patients whose condition is complicated by cardiac pathology. However, the pharmacologic superiority of levalbuterol over racemic albuterol remains a controversial and scientifically open question that awaits resolution by trial or the test of time with continued therapeutic use.

## Disclosure

Dr. Ameredes has served as a consultant and has received a research grant from Sepracor.

Dr. Calhoun has served as a consultant for Sepracor.

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